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PTEN, PAX2 and PINCH protein expression in normal endometrium, endometrial hyperplasia, and endometrioid adenocarcinomas

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Abstract

Aim: The purpose of this study was to investigate the role of PTEN, PAX2 and PINCH protein expressions in endometrial carcinogenesis. Material and Method: In this study 27 proliferative endometrium, 24 complex atypical hyperplasia, 10 complex hyperplasia without atypia, 30 simple hyperplasia without atypia, and 89 endometrioid type endometrial adenocarcinoma cases were enrolled. PTEN, PAX2 and PINCH antibodies were applied immunohistochemically to these cases. Results: Results of immunohistochemical staining revealed that during progression from normal to malignancy, staining distribution and intensity of both PTEN and PAX2 were found to decrease significantly. Expression of PINCH, on the other hand, was found to be increased distinctly during progression from normal to malignancy which correlated reversely with PAX2 and PTEN expressions. When PTEN, PAX2 and PINCH expressions in endometrioid adenocarcinoma cases were compared with common histopathologic prognostic parameters, a relation between histopathologic grade, angiolymphatic invasion, lymph node metastasis, stage, myometrial invasion and involvement of corpus cervix margin was not detected. Discussion: In conclusion, we suggest that the absence of PTEN and PAX2 expression seem to be associated with the progression of endometrioid carcinomas. Expression of PINCH, on the other hand, was found to be increased distinctly during progression from normal to malignancy. Further studies are necessary to define the biological role of PTEN, PAX2, and PINCH. PTEN, PAX2, and PINCH may have prognostic importance and predictive value for targeted therapies. Those expression profiles of biomarkers might also be expected to identify those patients with endometrial hyperplasia who are at risk of developing carcinoma.

Keywords

PTEN; Immunohistochemistry; Endometrial Carcinoma; PAX-2; PINCH-1PTEN

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Introduction

Endometrial adenocarcinoma is the most frequent malignancy of female genital system [1]. Two different clinicopathological subtypes are recognized: the oestrogen-related (type I, endometrioid) and the non-estrogen related (type II, non-endometrioid). It is assumed that type I, endometrioid tumors could develop on the basis of endometrial hyperplasia. A thorough understanding of the pathophysiology, including the molecular changes which occur during the transition from normal endometrium to carcinoma, allows clinicians to identify women at increased risk, and aim to facilitate early diagnosis. Identification of tumor markers associated with different types of endometrial carcinomas should help to identify exact molecular changes in these tumors. It has been shown that endometrioid (type I) carcinomas are associated with mutations in PTEN (phosphatase and tensin homolog deleted on chromosome 10), KRAS, CTNNB1, and PIK-3CA, and microsatellite instability, whereas non-endometrioid, type II carcinomas show HER2 amplification and recurrent TP53 mutations [2]. However, it is assumed that there are several potential oncogenic markers associated with the tumorogenesis of endometrial cancer.

Loss of PTEN activity can cause an increase in cell proliferation, escape from apoptosis, as well as an increase in survival through modulation of signal transduction pathways [3, 4]. Inactivation of PTEN tumor suppressor gene has been associated with endometrial carcinoma and its precursor, atypical endometrial hyperplasia [5]. PAX2 (Paired-box 2) is a member of the paired box gene family and acts as a tumor suppressor. PAX2 has been identified in renal cell carcinoma, nephrogenic adenoma and, serous carcinoma of the ovary. There is some data which suggest the loss of PAX2 function occurs in endometrial malignant transformation [6]. PAX2 and PTEN seem to be inactivated independently in non-neoplastic normal endometrium; concomitant inactivation of these genes does occur in the same gland could promote neoplastic transformation [7].

Cysteine-histidine rich protein (PINCH) is a member of the LIM protein family and is upregulated in tumor-associated stroma of several common types of cancers. To our knowledge, there is only one study investigating the relationship between PINCH and endometrial adenocarcinomas and PINCH expression was significantly increased in the stroma of these tumors as compared to the normal endometrium and atypical hyperplasia [8].

The purpose of this study was to compare the expression patterns of PTEN, PAX2 and PINCH proteins with other clinicopathologic prognostic variables in patients with normal endometrium, endometrial hyperplasia, and endometrioid adenocarcinomas.

Material and Method

Tissue samples were obtained from endometrial biopsy specimens and uterine resections; 27 proliferative endometrium, 24 complex atypical hyperplasia, 10 complex hyperplasia without atypia, 30 simple hyperplasia without atypia, and 89 endometrioid adenocarcinoma cases who were diagnosed between 2005-2011 at the Department of Pathology, Gazi University Faculty of Medicine, were included the study. Diagnosis of endometrioid adenocarcinoma was based on the FIGO (International Federation of Gynecology Obstetrics) Surgical Staging System for Endometrial Cancer (2009). Patient records were analyzed for age, FIGO stage, histologic grade, histologic type, depth of myometrial invasion and angiolymphatic invasion. All microscopic slides were re-evaluated and graded by two pathologists (E.K and O.E.). Approval for the study was given by the Ethical Committee of our Faculty of Medicine (2010-178).

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tissues. Hematoxylin and eosin stained sections were used to select a representative area of the tumor. Tissue sections were then used for immunohistochemical staining with PTEN/ MMAC1 Ab4/17a (mouse monoclonal antibody clone: 17A, Thermo Scientific/Neomarkers, USA), PINCH/LIMS1 (rabbit polyclonal, clone: GTX114984, Genetex, USA) and PAX2 /ep3251 antibody (rabbit monoclonal, clone: ab79389, Abcam, USA). After blocking endogenous peroxides and proteins, primary antibodies were applied for 2 hours for PTEN at 4ºC and overnight for PAX2 and PINCH at room temperature. The standard streptavidin-biotin indirect method was used. AEC (aminoethyl-carbazol) was used as a chromogen. Proliferative endometrium (for PTEN) and normal kidney tissue (for PAX2 and PINCH) were used as positive controls. Negative controls were incubated with PBS instead of the primary antibody.

Evaluation of immunohistochemical staining

The sections were microscopically examined and scored independently by the 2 pathologists (E.K and O.E) without any information on the clinicopathological data. Each section was first scanned with a low magnification, and then at least 10 fields were assessed with a high-power magnification. Cytoplasmic or nuclear staining was considered positive for PTEN, cytoplasmic and membranous staining was considered positive for PINCH and nuclear staining was considered positive for PAX2. The expression of PINCH was present in the cytoplasm of stromal fibroblasts/myofibroblasts and on the membrane of the epithelial cells of the endometrium. The staining was evaluated in the stromal fibroblasts/myofibroblasts. PTEN and PAX2 were present in the epithelial cells of the proliferative endometrium, endometrial hyperplasia, and carcinoma. The percentage of positively stained areas and staining intensity were recorded for all cases for PTEN, PAX2, and PINCH. The percentage of stained cells was classified as 0 for no staining, 1 for %1-11, 2 for %12-33, 3 for %34-66 and 4 for %67-100, regardless of the staining intensity. The intensity of staining was graded as 0 for negative staining, 1 for weak, 2 for moderate and 3 for strong, regardless of the staining percentage.

Data were analyzed by using "SPSS for Windows, v.10.0" (SPSS; Chicago, IL, USA) software. A comparison of groups was performed using Pearson's chi-square test and Fisher exact test. Continuous variables were expressed as the mean ± standard deviation, and categorical variables were expressed as frequency and percentage. Survival analysis was performed by Kaplan-Meier method. $P<0.05$ was considered as statistically significant.

Results

PTEN and PAX2 were present in the epithelial cells of endometrial glands and were highly expressed in the proliferative endometrium. Proliferative endometrium showed statistically

significant stronger staining for PAX2 when compared with endometrioid adenocarcinomas (p<0.001, Table 1). Concomitantly loss of PAX2 and PTEN expression was detected in precancers and carcinoma. Both PAX2 and PTEN expression in endometrioid carcinomas was similar to that in atypical hyperplasias (p>0.05, Table 2).

Table 1. Distribution of groups according to staining extent of the PTEN, PAX2 and PINCH antibodies

Groups according to the extent of staining.		Proliferative Endometrium			Hyperplasia without atypia			Atypical endometrial hyperplasia			Endometrioid Carcinoma		
		n	%	p values[1]	n	%	p values[1]	n	%	p values[1]	n	%	p values[1]
PTEN	0							2	8,3		21	23,6	
	1	1	3,7		1	2,5					24	27	
	2			<0.001	9	22,5	<0.001	12	50	<0.001	28	31,5	<0.001
	3	3	11,1		26	65		10	41,7		16	17,9	
	4	23	85,2		4	10							
PAX2	0							1	4,2				
	1										14	15,7	
	2	2	7,4	<0.001	4	10	<0.001	8	33,3	<0.001	51	57,3	<0.001
	3	10	37,0		17	42,5		8	33,3		22	24,7	
	4	15	55,6		19	47,5		7	29,2		2	2,2	
PINCH	0	1	3,7										
	1	6	22,2		13	44,8		3	12,5		1	1,1	
	2	18	66,7	<0.001	24	82,8	<0.001	14	58,3	<0.001	28	31,5	<0.001
	3	2	7,4		2	6,9		4	16,7		37	41,6	
	4				1	3,4		3	12,5		23	25,8	

Table 2. Distribution of groups according to staining intensities of the PTEN, PAX2 and PINCH antibodies

n	Distribution of staining intensities according to groups.	Proliferative Endometrium			Hyperplasia without atypia			Atypical endometrial hyperplasia			Endometrioid Carcinoma		
		%	p values[1]	n	%	p values[1]	n	%	p values[1]	n	%	p values[1]	
PTEN	0-1	1	3,7		2	5		7	29,2		50	56,2	
	2	2	7,4	<0.001	19	47,5	<0.001	17	70,8	p=0.14	34	38,2	<0.001
	3	24	88,9		19	47,5					5	5,6	
PAX2	0-1	2	7,4		4	10		6	25		48	53,9	
	2	9	33,3	<0.001	13	32,5	<0.001	10	41,7	p=0.19	29	32,6	<0.001
	3	16	59,3		23	57,5		8	12,5		12	13,5	
PINCH	0-1	22	81,5		29	72,5		11	45,8		13	14,6	
	2	5	18,5	<0.001	10	25,0	<0.001	10	41,7	p=0.2	44	49,4	<0.001
	3				1	2,5		3	12,5		32	36,0	

[1]: Statistical comparison with endometrioid carcinoma

PINCH staining was observed in both glandular and stromal compartments and was localized in both cytoplasm and membranous components. Expression of PINCH was increased in endometrioid carcinoma as compared to the proliferative endometrium (p<0.001). PINCH expression in endometrioid carcinomas was similar to that in atypical hyperplasias (p=0.2). Distribution of groups according to staining extent and intensities of the PTEN, PAX2 and PINCH stainings are given in Tables 1-2. The results of PTEN, PAX2 and PINCH immunoreactivity in normal, hyperplastic, and malignant endometrium are shown in Figure 1-3.

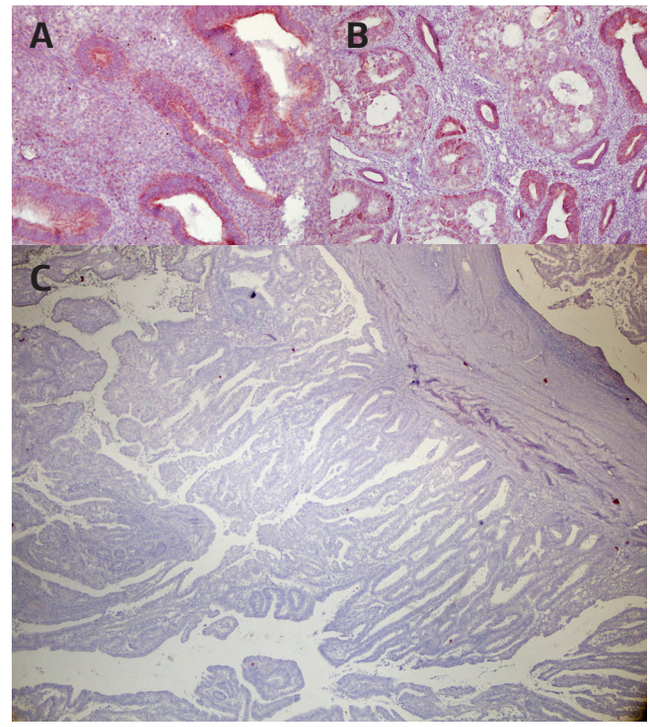

Figure 1. PTEN expression (A, X400) simple hyperplasia without atypia: strong positivity of PTEN in glands and stroma, (B, X100) complex atypical hyperplasia (PTEN loss, heterogeneous) (C, X100) in this case, the vast majority of the tumor is PTEN negative.

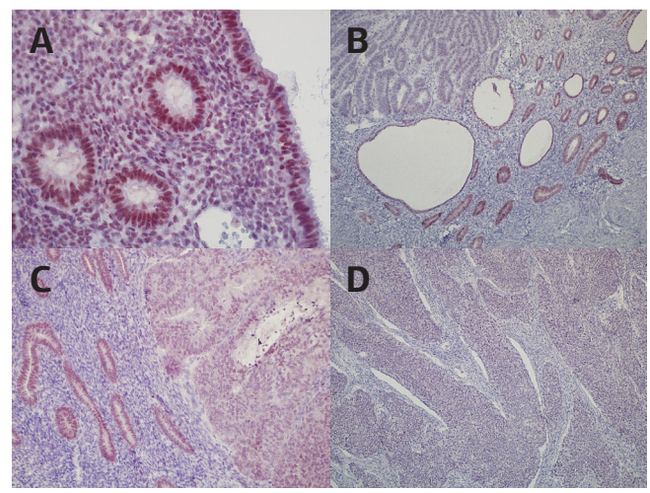

Figure 2. PAX2 expression (A, X400) proliferative phase endometrium, (B,C, X100) hyperplasia and (D, X100) endometrioid carcinoma

Results of immunohistochemical staining revealed that during progression from normal to malignancy, staining distribution, and intensity of both PTEN and PAX2 were found to decrease significantly. Expression of PINCH, on the other hand, was found to be increased distinctly during progression from normal to malignancy which correlated reversely with PAX2 and PTEN expressions. When PTEN, PAX2 and PINCH expressions in endo-

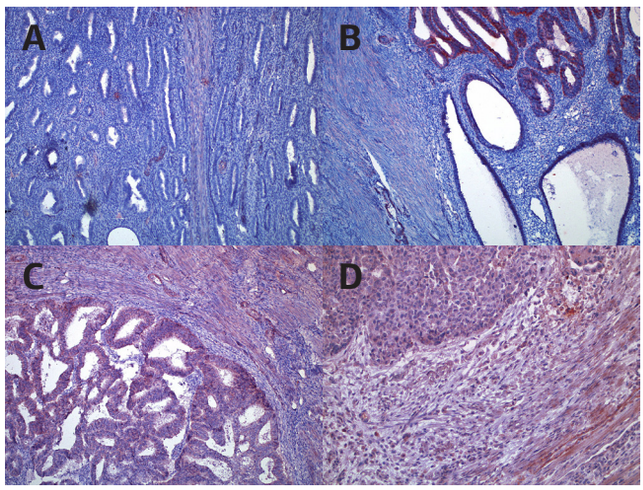

Figure 3. PINCH expression (A, X100) proliferative phase endometrium, (B,C, X100) hyperplasia and (D, X100) endometrioid carcinoma

metrioid adenocarcinoma cases were compared with common histopathologic prognostic parameters, a relation between histopathologic grade, angiolymphatic invasion, lymph node metastasis, stage, myometrial invasion, and involvement of corpus cervix margin was not detected (p>0.05, Table 3).

Discussion

PTEN has been well recognized as a tumor suppressor gene which acts as a critical negative regulator of the ubiquitous PI3K pathway that transduces signals regulating growth, proliferation and survival signals regulating growth, proliferation, and survival [9]. In addition to endometrial cancer, PTEN is mutated or deleted in a variety of cancers, including glioblastoma, cancers of breast, thyroid, lung, ovary, and prostate [10-15]. PTEN gene mutations are seen in 18-55% of endometrial precancers, 26-80% of endometrioid adenocarcinomas [16].

Akiyama-Abe et al. reported that expression of PTEN was lost in 56 endometrial carcinoma patients (25%) [17]. Heejeong et al. showed that PTEN loss was significantly higher in endometrial carcinoma compared with simple hyperplasia (68% vs. 24%), and it was also higher in complex atypical hyperplasia compared with simple hyperplasia (71% vs. 24%) [18]. In our study, PTEN expression in endometrioid carcinomas was similar to that in atypical hyperplasias (p=0.14), suggesting that alterations in PTEN occur at a relatively early stage in endometrial tumorigenesis.

PAX2 is a transcription factor and a member of the paired box gene family (PAX1 to PAX-9). Although these proteins are especially expressed during the embryonic development and organogenesis, it has been demonstrated that PAX proteins play a critical role in various types of malignancy [6]. Allison et al. evaluated 206 endometrial samples and found that the percentage of cases with complete PAX2 loss increased with increasing severity of hyperplasia ant partial loss of PAX2 expression did occur in normal endometrium (17.9%) but in smaller proportions of tissue and was less frequent than in simple hyperplasia (47.8%), complex hyperplasia (32.5%), atypical hyperplasia (22.2%), and FIGO grade 1 carcinomas (20.0%). PAX2 loss in endometrial hyperplasia occurred early in the spectrum of hyperplasia and became more frequent and complete with increasing severity of endometrial pathology [19]. Kahraman et al. showed that the mean percentages of PAX2 staining cells were 80.8, 96.7, 88.6, 92.7, and 99.2 with proliferative endometrium, atrophic endometrium, complex hyperplasia, complex atypical hyperplasia, and adenocarcinoma, respectively. Similar to our study, they did not find any correlation between PAX2 expression levels and the stage, histological grade, myometrial invasion, and lymph node status in cancer cases [20].

We investigated the correlation of expression of PTEN and PAX2. The results of our study showed that in endometrial lesions PTEN expression correlated with PAX2 expression. Monte et al. showed that coincident loss of PAX2 and PTEN expression in normal endometrium was seen in 21% of patients, but usually involved different glands. The coincident loss was more common in precancers (31%) and carcinomas (55%) [7].

Table 3. Distribution of PTEN, PAX2, and PINCH antibody staining intensities in relation to demographic and prognostic features.

		PTEN			p values	PAX2			p values	PINCH			p values
Feature		0-1	2	3		0-1	2	3		0-1	2	3	
	1	44	34	5		43	29	11		10	43	30	
Stage	2	3			0,285	3			0,317	2	1		0,036
	3	3				2		1		1		2	
	1	14	10	1		13	10	2		7	11	7	
Histological grade	II	29	21	3	0,928	30	16	7	0,565	5	29	19	0,159
	III	7	3	1		5	3	3		1	4	6	
	<%50	28	26	4		33	20	5		7	33	18	
Myometrial invasion	>%50	17	5		0,173	10	5	7	0,056	4	7	11	0,343
	None	5	3	1		5	4			2	4	3	
	Present	9	3			5	2	5		1	5	6	
Angiolymphatic invasion	None	41	31	5	0,319	43	27	7	0,008	12	39	26	0,521
	None	4	5	2		5	5	1		5	5	1	
lymph node metastasis	None	42	27	3	0,304	40	23	9	0,526	7	38	27	0,008
	Present	4	2			3	1	2		1	1	4	
	None	40	31	5		39	26	11		11	36	29	
Involvement of corpus cervix margin	Present	10	3		0,231	9	3	1	0,482	2	8	3	0,56

PINCH (LIMS1) is a family of cell extracellular-matrix (ECM) adhesion proteins and is in interaction with integrin-linked kinase (ILK), an integrin-binding protein [21]. PINCH and ILK play a key role in facilitating various cell signaling intermediates of the survival pathway. Lincoln et al. demonstrated that ILK is critical for the PTEN-sensitive regulation of phosphatidylinositol-3'-kinase (PI3K)/Akt pathway dependent cell cycle progression. PINCH-ILK is related to PTEN by the PI3K signaling pathway [22]. Previous studies reported PTEN mutation in endometrial carcinomas. To our knowledge, there is only one study investigating the relationship between PINCH and endometrial adenocarcinomas. Recently, Zhang et al. first reported PINCH protein expression in normal endometrium, atypical endometrial hyperplasia, and endometrial cancer. It was reported that the PINCH is expressed in the endometrial glandular cells and fibroblasts/myofibroblasts in the tumor stroma. Zhang et al. detected that PINCH was strongly expressed in tumor-associated stroma [8]. We also have found that expression of PINCH was increased in endometrioid carcinoma as compared to the proliferative endometrium ($p<0.001$). PINCH expression in endometrioid carcinomas was similar to that in atypical hyperplasias ($p=0.2$).

Conclusion

In conclusion, we suggest that the absence of PTEN and PAX2 expression seem to be associated with the progression of endometrioid carcinomas. Expression of PINCH, on the other hand, was found to be increased distinctly during progression from normal to malignancy. Further studies are necessary to define the biological role of PTEN, PAX2, and PINCH. PTEN, PAX2, and PINCH may have prognostic importance and predictive value for targeted therapies. Those expression profiles of biomarkers might also be expected to identify those patients with endometrial hyperplasia who are at risk of developing carcinoma.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

The authors declare that they have no competing interests.

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